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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,295	09/09/2002	Menachem Rubinstein	RUBINSTEIN=7	2828

1444 7590 09/28/2006

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EXAMINER	
CHANDRA, GYAN	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 09/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,295	RUBINSTEIN ET AL.	
	Examiner	Art Unit	
	Gyan Chandra	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,9 and 11-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,9 and 11-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

Claims 1-4, 6-8, and 10 are canceled.

The addition of new claims 12-18 has been made of record.

Claims 5, 9 and 11-18 are pending.

Claims 5, 9 and 11-18 are examined on the merit to the extent that they read on the elected invention of VEGF inhibitor – CSC.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Claim Objection

The objection to claim 5 has been withdrawn due to applicant's amendment to the claim.

Claim Rejections - 35 USC § 112-written description

Claims 5, 9 and 11-18 stand rejected under 35 U.S.C. 112, first paragraph-written description for the reasons of record mailed on 2/13/2006.

The claims are drawn to a method for inhibiting angiogenesis in mammals comprising administering subject a pharmaceutical composition comprising (i) leptin, (ii) a leptin homolog having 80% sequence identity with the sequence of leptin, (iii) a leptin homolog having 90% sequence identity with sequence of leptin or (iv) a derivative of leptin or leptin homolog.

Applicants argue that the specification cites GB229282 (WO 96/05309) that providing support for the disclosure of leptin and analog thereof. Applicant argues that one skilled in the art can make leptin homolog and derivatives of leptin from the cited art. Further, applicant argues that one skilled in the art can make a leptin homolog with 80% or 90% sequence identity to the leptin sequence that comprises activities similar to wild type leptin.

Applicants' arguments have been fully considered but they are not persuasive because the specification does not provide any definition of leptin derivative. The claims do not require that the leptin homologue or derivative possess any particular conserved structure, or any other disclosed distinguished feature. Thus the claims are drawn to a genus of polypeptides variant or derivative that is defined by a large number of amino acid substitutions, deletions, insertions or chemical modifications that can reversibly inhibit endothelial cell proliferation.

The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, method of making an invention or any combination thereof. One skill in the art would not know which 10 or 20% amino acids of leptin sequence should be substituted, mutated, deleted or inserted to retain substantially leptin like activity. Therefore, to provide possession of the claimed invention, the specification must provide sufficient distinguishing identifying characteristics for the invention.

Claim Rejections - 35 USC § 112-enablement

Claims 5, 9 and 11-18 stand rejected under 35 U.S.C. 112, first paragraph-enablement for the reasons of record mailed on 2/13/2006.

Claims 5, 9 and 11-18 are drawn to a method for inhibiting angiogenesis in mammals comprising administering subject a pharmaceutical composition comprising (i) leptin, (ii) a leptin homolog having 80% sequence identity with sequence of leptin, (iii) a leptin homolog having 90% sequence identity with sequence of leptin or (iv) a derivative of leptin or leptin homolog.

Applicants argue that they have amended the claims which are directed towards inhibiting angiogenesis and not "reversible inhibition of angiogenesis". Applicants cite a post filing art by Cohen et al to support the enablement of the instant invention.

Applicants' arguments have been fully considered but they are not persuasive because the specification discloses that the administration of leptin inhibits angiogenesis in ob -/- mouse but not in normal mouse [Example 1, page 24]. Similarly, Cohen et al teach induction of apoptosis and the induction of expression angiopoietin-2 by administering leptin to 8-10 week old obese (C57Bl –0b/0b) female mice lacking endogenous leptin production (pg. 7697-7698, Results). Further, on page 7698, Cohen et al teach that in mice (ob/ob) and C57Bl (-db/db) mice lacking the long form leptin receptor, the expression of Ang-2 mRNA in adipose tissue was not mediated through leptin. Thus far, the art does not provide any clear guidance on leptin's role in inhibiting angiogenesis.

Ring et al. (previously presented) teach that leptin promotes wound heeling in a dose dependent manner by interacting with its receptor. Teichert-Kuliszewska et al. teach that Ang-1 and Ang-2 play a balancing act in endothelial cell proliferation. Hegen et al (Art. Thromb. Vasc. Biol. 24: 1803-1809, 2004) suggest that Ang2 may play role in angiogenesis inhibition and that a number of growth factor and cytokine activate the expression of Ang-2 gene (pg. 1808, right side column). Therefore, the role of leptin, leptin homolog or leptin derivatives in angiogenesis inhibition is unpredictable, therefore, this would require large amount experimentation to determine if leptin could inhibit angiogenesis in mammals.

Even if the administration of leptin inhibits angiogenesis, the specification does enable one of skill in the art for inhibiting angiogenesis by administering leptin homologues having 80% or 90% sequence homology with leptin sequence. The specification fails to disclose any leptin homologue or leptin derivative which is capable of inhibiting angiogenesis in normal mice. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinants to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively

conservative substitutions or no substitution (see Bowie et al., 1990, Science 247: 1306-1310, page. 1306, column 2, paragraph 2; Wells, 1990, Biochemistry 29:8509-8517).

New Rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 9, the phrase "substantially similar activity" renders the claim indefinite because it is unclear how similar is leptin homolog to leptin activities. Does the homolog comprise the same activity as leptin has or it has only 80% or 90% of leptin's activity? Therefore, the metes and bounds of the claim cannot be determined.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571) 272-2922. The examiner can normally be reached on 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Art Unit 1646
12 September 2006
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Eileen B. O'Hara

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PRIMARY EXAMINER